What is the Optimal Antithrombotic Therapy after PAD Revascularization in 2021?

Take-home Messages:

- Medications for peripheral vascular disease have been understudied relative to those for other domains in cardiology.

- The long-standing approach for patients with symptomatic peripheral artery disease (PAD) is to start antiplatelet therapy at the time of diagnosis.
- Most data to support aspirin is based on a collaborative meta-analysis that showed some benefit in subsets of populations with PAD, as well as extrapolation

from literature on coronary artery disease and the concept of secondary prevention.

- The CAPRIE trial showed that clopidogrel was superior to aspirin in reducing the aggregate measure of myocardial infarction, ischemic stroke, and vascular death, particularly in patients with PAD. Current guidelines show

that clopidogrel and aspirin are equivalent for secondary prevention in patients with symptomatic PAD.

- The EUCLID trial showed no benefit for ticagrelor over clopidogrel for reducing the incidence of cardiovascular events in patients with symptomatic PAD.
- The PEGASUS-TIMI 54 trial, which compared

long-term use of ticagrelor plus aspirin with placebo plus aspirin in patients with prior myocardial infarction to prevent recurrence of ischemic events, showed benefits that were concentrated in patients with PAD, suggesting a role for ticagrelor in addition to aspirin in this setting.

- The COMPASS trial examined the role of adding rivaroxaban 2.5 mg twice per day to aspirin for preventing long-term cardiovascular events in patients with stable atherosclerotic vascular disease.
  - A preplanned substudy of patients with PAD showed a reduction in major adverse

cardiovascular events and major adverse limb events with the addition of rivaroxaban 2.5 mg twice per day to aspirin.

- The VOYAGER-PAD trial randomized patients undergoing an endovascular or surgical revascularization procedure in the lower extremities to receive

rivaroxaban 2.5 mg twice per day with aspirin or placebo with aspirin (clopidogrel could also be used in either group at the investigator's discretion).

- Rivaroxaban plus aspirin reduced the long-term risk for cardiovascular and limb-related events, including arterial thrombosis and

embolism, after peripheral revascularization compared with aspirin plus clopidogrel and aspirin alone, respectively.

- A slight increase in bleeding was observed, but this was observed primarily when clopidogrel was added to rivaroxaban and aspirin.

- Although rivaroxaban with aspirin appears to be the optimal antiplatelet-antithrombin regimen for patients who have symptomatic PAD or are undergoing a peripheral vascular intervention, data on dual antiplatelet therapy are from subanalyses of other studies in the PAD space.

- The CHARISMA trial showed that patients, particularly those with peripheral vascular disease, benefitted more from clopidogrel plus aspirin than from aspirin alone.
- A study that evaluated patients with PAD who underwent coronary stenting showed a reduction in cardiovascular events

among patients with diagnosed PAD who were on aspirin and dual antiplatelet therapy (primarily clopidogrel).

- Although data suggest that dual antiplatelet therapy benefits patients in the long term, none of the studies primarily randomized patients with PAD.

- Outside of the periprocedural period, where dual antiplatelet therapy is used 1 to 2 months after a peripheral stent or drug-coated balloon, the strongest data are for rivaroxaban 2.5 mg with aspirin. Dual antiplatelet therapy is not usually continued long term in this population due to a

lack of supporting evidence.

- The cardiologist should know that generally all patients with PAD should receive antiplatelet agents (aspirin 81 mg/ day is usually preferred, although clopidogrel is a reasonable alternative). Rivaroxaban 2.5 mg/ day is an important addition to aspirin in patients with

polyvascular disease or high-risk features (eg, diabetes), although bleeding risks and polypharmacy are important to consider.

References

1. **Bauersachs RM, Szarek M, Brodmann M, et al.** Total ischemic event reduction with rivaroxaban after peripheral arterial

revascularization in the VOYAGER PAD trial. *J Am Coll Cardiol*. 2021;78(4):317-326.

2. **Bonaca MP, Bhatt DL, Storey RF, et al.** Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol*. 2016;67(23):2719-2728.

3. **Hiatt WR, Fowkes FG, Heizer G, et al.** Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376(1):32-40.

4. **Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA.** The COMPASS trial: net clinical benefit of low-dose rivaroxaban plus aspirin as

compared with aspirin in patients with chronic vascular disease *Circulation*. 2020;142(1):40-48.